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Research Report

Oxytocin and the social brain: Neural mechanisms and perspectives in human research

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ABSTRACT

The present paper summarizes functional imaging studies investigating the effects of intranasal oxytocin (OT) on brain responses to social stimuli. We aim to integrate previous research, point to unresolved issues and highlight perspectives for future studies. The studies so far have focused on identifying neural circuits underlying social information processing which are particularly sensitive to modulations by exogenous OT. Most consistently, stimulus-related responses of the amygdala and associated areas within the prefrontal and temporal cortices have been found to be modulated by OT administration. However, there are a number of unresolved issues related to the possible role of sex differences and hormonal status, genetic variability, and individual differences in socio-cognitive functioning. Future studies focusing on these open questions are expected to contribute to a more nuanced understanding of the role of the central OT system in humans and may provide the basis for novel treatment approaches for mental disorders characterized by social deficits.

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1. Introduction

1.1. *The role of oxytocin in human social cognition and behavior*

Within the last decade, the neuropeptide oxytocin (OT) has attracted increasing attention. Its importance for species-specific social functioning was first revealed by animal studies demonstrating that central OT receptor distribution critically determines several aspects of social behavior such as pair bonding and parental care (e.g. Insel and Young, 2001; Young and Wang, 2004).

In humans, most studies investigating the behavioral and neural effects of OT have used placebo-controlled intranasal application. The rationale for this approach is based on findings that neuropeptides are capable of reaching the central nervous system following intranasal administration (Born et al., 2002). An actual increase in central OT levels following intranasal OT administration was recently confirmed by microdialysis in relevant brain regions of rats and

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mice (Neumann et al., in press). Studies that have explored associations of peripheral OT levels with social stimulus processing are highly controversial regarding the validity of the assessment and interpretation with respect to CNS availability of the neuropeptide and need further investigation (Anderson, 2006; Horvat-Gordon et al., 2005; Landgraf and Neumann, 2004; Carter et al., 2007; for an overview, see Heinrichs et al., 2009).

To date, effects of OT on human social cognition and behavior have been summarized in several reviews and meta-analyses (e.g. Heinrichs and Domes, 2008; Heinrichs et al., 2009; Shahrestani et al., 2013; Striepens et al., 2011). The main body of empirical evidence so far suggests beneficial effects of intranasal OT on several aspects of social information processing and social behavior including eye gaze, facial emotion recognition, social reward processing and trust (for recent reviews, see Guastella and MacLeod, 2012; Meyer-Lindenberg et al., 2011; Shahrestani et al., 2013; Van IJzendoorn and Bakermans-Kranenburg, 2012). Together with results from animal studies, these findings point to the therapeutic potential of interventions in the central nervous OT system for the treatment of mental disorders characterized by social impairments like social anxiety, schizophrenia or autism spectrum disorders (for recent reviews, see Meyer-Lindenberg et al., 2011; Modi and Young, 2012; Striepens et al., 2011). Despite substantial evidence for beneficial effects of OT on social behavior, the neural mechanisms underlying these effects are still not well understood in humans.

1.2. *The oxytocin system in the human brain*

In rats, OT receptors are highly expressed in olfactory and hypothalamic regions, structures of the limbic system (e.g. amygdala), the thalamus, basal ganglia, as well as in the brain stem and spinal cord (for a review, see Gimpl and Fahrenholz, 2001). OT binding sites in humans, however, remain rather elusive. Preliminary results suggest that OT receptor distribution in the human brain differs substantially from other species with higher densities in dopaminergic neurons of the substantia nigra and the cholinergic nucleus basalis of Meynert (Loup et al., 1991). However, Gimpl and Fahrenholz (2001) point to the possibility that high levels of OT in one region might decrease local OT receptor expression to an extent that does not allow for detection by common methods like radioligand-based autoradiography. Thus, radioligands for in vivo PET studies in humans are still needed to provide a better understanding of OT receptor distribution in the human brain.

While mapping of OT receptors in the human brain is still in its infancy, functional brain imaging techniques allow for mapping of brain regions potentially mediating the effects of OT on human cognition and behavior. Some studies have explored OT effects on brain activation using EEG or MEG (Bick et al., 2013; Herzmann et al., in press; Hirosawa et al., 2012; Huffmeijer et al., 2013, 2012; Perry et al., 2010; Sheng et al., 2013). These methods have high temporal but rather low spatial resolution, which complicates localization of neural networks associated with the cognitive process under study, especially if the brain areas of interest are located subcortically. In comparison, spatial resolution is much higher in functional magnetic resonance imaging (fMRI), the most commonly used brain imaging tool in human OT research.

1.3. *Aims and structure of this article*

Here, we aim to provide a critical reflection on the current state of fMRI findings in OT research and highlight methodological challenges and open questions that should be addressed by future studies. We will start with a short review of selected fMRI studies integrating most of the previous evidence for effects of intranasal OT on neural correlates of social cognition and behavior (Table 1). In the majority of these studies, a single dose of OT was administered to healthy individuals following a randomized, placebo-controlled, experimental protocol. The cognitive functions under study included face perception and emotion processing (Domes et al., 2010a, 2007; Gamer et al., 2010; Kirsch et al., 2005; Lischke et al., 2012; Petrovic et al., 2008; Rupp et al., 2012), proxies of parental sensitivity and attachment (Riem et al., 2012, 2011; Rupp et al., 2013; Wittfoth-Schardt et al., 2012), as well as different aspects of social feedback processing (Baumgartner et al., 2008; Groppe et al., 2013; Rilling et al., 2012). So far, few studies have focused on potential effects of intranasal OT on brain responses in clinical samples characterized by social deficits such as social anxiety (Labuschagne et al., 2011, 2010), borderline personality disorder (Bertsch et al., in press), or autism spectrum disorders (Domes et al., 2013a, in press; Watanabe et al., in press).

2. Effects of OT on neural correlates of face perception and emotion processing

2.1. *The neural basis of social threat processing and anxiolytic effects of OT*

Results from both animal studies and human behavioral studies have consistently indicated anxiolytic effects of OT (e.g. Bale et al., 2001; Heinrichs et al., 2003; Huber et al., 2005; Viviani et al., 2011). An initial fMRI study therefore focused on OT effects on neural responses to threatening scenes and facial expressions (Kirsch et al., 2005). Compared to placebo, intranasal administration of OT dampened amygdala reactivity to negative social cues and reduced functional coupling of the amygdala with brainstem regions. These results correspond to recent findings from animal studies indicating that OT decreases behavioral fear responses by modulating amygdala signaling to brainstem regions (Knobloch et al., 2012; Viviani et al., 2011).

To gain a better understanding of potential anxiolytic OT effects in humans, a later fMRI study combined intranasal OT administration with a fear-conditioning paradigm in which neutral facial expressions were paired with electric shocks (Petrovic et al., 2008). After conditioning, participants were administered a single dose of OT and underwent fMRI scanning during which they viewed the same faces with shock electrodes applied. OT attenuated changes in affective stimulus ratings following fear conditioning and reduced neural responses to conditioned as compared to unconditioned stimuli in the amygdala, the medial temporal gyrus and the anterior cingulate cortex. These structures are discussed as part of a neural alarm